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Polyethylene Glycol-Polyvinyl Alcohol Graft Copolymer: A Peroxide-Free Binder

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Print

Introduction

Excipients are integral components of solid oral dosage formulations (SODF). Therapeutic efficacies of these dosages are dependent upon the excipients' function and method of use, and also their interactions with active ingredients (APIs)[1]. These excipients, commonly used as fillers, binders, disintegrants and/or coatings in tablets and pellets, contribute to the dosage's shape and size, delivery and stability[2]. Formulation technologies are as important as excipient selection and both contribute to delivery and stability of APIs in the dosages[3]. Therefore, the efforts continue to identify the appropriate excipients in the development of stable and efficacious SODFs amenable to desired formulation platforms or technologies accepted by the industry.

Granulation is widely used in the development of pharmaceutical dosages[4-6]. Wet granulation, in particular, is still commonly practiced in the industry especially for achieving the good content uniformity of low dose drugs. There is a range of excipients thus used as wet binders in SODF including povidone, copovidone, hydroxypropyl cellulose, hypromellose and starch derivatives. These excipients, depending upon their structures and functions, and the source of origins, contain inherent impurities such as peroxides, heavy metals, and aldehydes among others, which could catalyze the degradation of APIs under storage and/or processing conditions[7-9].

The source of residual peroxides in these excipients might be the result of either the use of catalysts or free radical initiators in the polymerization or air-borne in nature. Therefore, controlling the peroxides either by applying a tailor-made manufacturing procedure or selecting an appropriate packaging or using a suitable antioxidants for these excipients, is crucial for maintaining the stability of APIs in the formulation dosages. These precautionary measures are highly warranted for highly oxidizable APIs to minimize or even alleviate the peroxides to help enhance the shelf life and maintain the efficacy of drug products. The direct contact of APIs with binders in SODF matrices brings a significant risk of altering the potency of drugs with uncontrolled peroxides. Therefore, the efforts continue to identify the optimal binder with outstanding binding properties and significantly low or no peroxides for the development of highly sensitive APIs.

This article focuses on polyethylene glycol based polyvinyl alcohol graft copolymer (Kollicoat® IR), referred as "PEG-PVA", which is primarily used as an instant release coating polymer, but will be examined again as a wet binder. The relevant physico-chemical properties and applications as a wet binder will be discussed. In addition, its safety and regulatory and pharmacopoeial status will also be reviewed and discussed.

Polyethylene Glycol-Polyvinyl Alcohol (PEG-PVA) Graft Copolymer

(Kollicoat® IR)

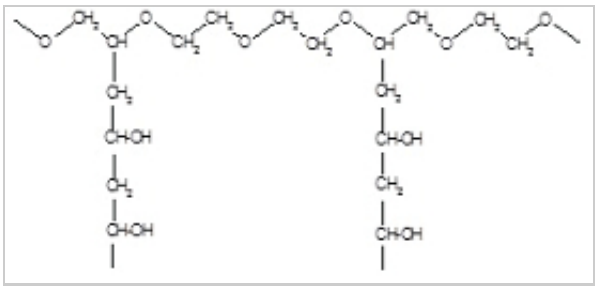

Figure 1. Structure of PEG-PVA copolymer

PEG-PVA is a hydrophilic freely water-soluble polymer, comprised of 25% PEG and 75% PVA, wherein the vinyl alcohol moieties are grafted on a polyethylene glycol backbone, as shown in *Figure 1*[10].

PEG-PVA is a spray dried powder of a high flowability recognizable by an angle of repose below 30°. The grafted PEG acts as a plasticizer, and hence provides a greater flexibility of films without additional plasticizers. PEG-PVA films with iron oxide red pigment are effective against transmission of light and meets the European pharmacopeia's requirement of colored light protecting glass containers[11]. The low viscosity of PEG-PVA even at higher solid contents in aqueous solutions, improves processing time and saves cost. *Table 1* lists some of the key attributes of this copolymer, which are critical in preparation of solutions for coating and wet granulation.

Table 1. Physio-chemical properties of PEG-PVA graft copolymer

Physico-chemical properties	
Molecular weight	45,000 Dalton
pH	5-8
k-value (1% water)	31-34
Solubility Water 0.08 N HCl (pH 1.2) Phosphate buffer, pH 6.8 Water/ethanol (1:1) Organic solvents	 >30 % >30 % >30 % 20% Insoluble
Viscosity at 20 wt% (water)	115 mPas
Oxygen permeability	104 $cm^3/100\ \mu m/m^2.d$
Water vapor permeability	510 $cm^3/100\ \mu m/m^2.d$
Elongation at break (film thickness 100 µm)	105% @ 54% RH
Disintegration time (film thickness 100 µm)	0:44 sec @ pH 1.2, pH 6.8
Dissolution time (film thickness 100 µm)	1:30 min @ pH 1.2, pH 6.8
Surface tension, 23 °C	10 wt% solution: 44 mN/m^2 20 wt% solution 41 mN/m^2
PEG (free)	None

Results

Formulation of placebo tablets with PEG-PVA as a binder

Table 2 shows the composition of excipients in individual placebo formulations comprised of PEG-PVA and povidone K30 (Kollidon® 30) as wet binders used at 3%, 4% and/or 5% in aqueous solution. Briefly, the blends of lactose monohydrate, MCC, and crospovidone were individually granulated with PEG-PVA or povidone K30 solution for 2-4 minutes, and the resulting granules were dried in a fluid bed at 50°C inlet air temperature resulting in a product temperature of 32°C, and subsequently sieved through an Alexanderwerk oscillator's screen (#20) before compressing into tablets on a Korsch XL100. Table 3 shows the particle size distribution of granules prepared with 3% and 4% povidone K30 and PEG-PVA as binders.

Table 2. Composition of formulations (F1-F5) used in wet granulation

Excipient, %	F1	F2	F3	F4	F5
Lactose monohydrate	72.5	71.5	72.5	71.5	69.5
MCC PH 102	20.0	20.0	20.0	20.0	20.0
Povidone K30	3.0	4.0	-	-	-
PEG-PVA			3.0	4.0	5.0
Kollidon® CL	5.0	5.0	5.0	5.0	5.0
Mg stearate	0.5	0.5	0.5	0.5	0.5

The granules prepared with povidone K30 and PEG-PVA were analyzed for their particle size distributions, and the results are summarized in *Table 3*.

Table 3. PSD of granules with 3% povidone K30 and 4% PEG-PVA

Binder	Screen, % residue						
	#20	#40	#80	#120	#200	#325	Fines
3% Povidone K30	0	8	46	12	14	8	3
3% PEG-PVA	0	10	43	11	15	8	2
3% Povidone K30	0	8	35	17	25	10	4
3% PEG-PVA	0	3	38	25	26	8	2

The bulk/tapped density and flowability of the granules containing PEG-PVA and povidone K30 as binders, and the resulting hardness (ca. 7-8 kP) derived from the tablets are summarized in *Table 4*. *Table 4* also shows the physical properties of granules, and the disintegration/ dissolution properties of tablets containing 3%, 4%, and/or 5% povidone K30 and PEG-PVA.

Table 4. Physical properties of placebo granules prepared with PEG-PVA and Povidone K-30

Formulation	Bulk density (g/ml) (granules)	Tapped density (g/ml) (granules)	Flowability, through # 5 ring	Tablet weight, mg	Thickness (mm)	Hardness (kP)*	Friability (%)	Disintegration time (min)
F1, 3% Povidone K30	0.53	0.64	Conform	426.6	4.5	7.7	0.12	0:11
F2, 4% Povidone K30	0.50	0.64	Conform	424.6	4.5	6.7	0.18	0:28
F3, 3% PEG-PVA	0.52	0.62	Conform	424.6	4.5	6.4	0.15	0:32
F4, 4% PEG-PVA	0.53	0.63	Conform	426.7	4.5	7.4	0.15	0:31
F5, 5% PEG-PVA	0.53	0.63	Conform	426.7	4.5	8.1	0.16	0:35
*Compression force 10 kN								

The granules were further evaluated for tablet properties (weight, thickness, hardness and disintegration time) by compression at 9 kN, 11 kN, 17 kN, 22 kN and 27 kN, which are summarized in *Table 5*. Interestingly, the tablet properties were in general very similar for all tablets prepared either with povidone K30 or PEG-PVA at all compression forces.

Table 5. Properties of tablets compressed at diff erent compression forces

Compression force (kN)	Povidone K30, 3% solution		PEG-PVA, 3% solution	
	Hardness (kP)	Disintegration time (min:sec)	Hardness (kP)	Disintegration time (min:sec)
9	6.6	0:26	4.2	0:38
11	8.4	0:25	9.6	0:34
17	11.4	0:40	12.2	0:49
22	12.6	0:47	13.8	1:24
27	12.7	1:08	14.6	1:27

Figure 2 illustrates that the hardness of tablets derived from PEG-PVA corresponds to that of povidone K30 and increased with increasing compression forces. At compression forces relevant for production PEG-PVA performed slightly better than povidone K30. As expected, the ejection force increased linearly as a function of compression force ranging between 75 N and 150 N at a compression force between 9 kN and 27 kN (data not shown).

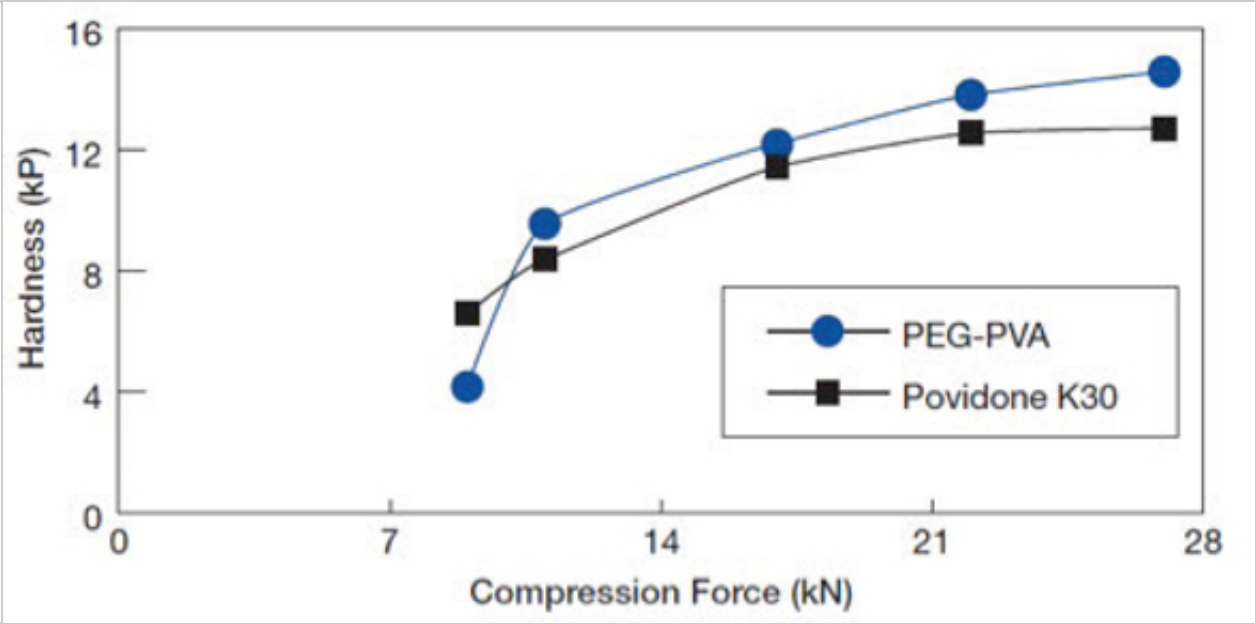

Figure 2. Hardness versus compression force of povidone K30 and PEG-PVA binders

Formulation of Ascorbic Acid Tablets with PEG-PVA as a Binder

PEG-PVA was also evaluated as a wet binder in mixer and fluid bed granulation at a 3% level in ascorbic acid tablets and placebo tablets, and compared with copovidone and HPMC Type 3. *Table 6* summarizes the list of ingredients used in placebo and ascorbic acid (Vitamin C) formulations[12].

Table 6. Composition of placebo and ascorbic acid tablets

Ingredient	Placebo tablet, mg	Ascorbic acid tablet, mg
Ascorbic acid	-	50
Corn starch	230	-
Lactose	230	130
MCC	-	130
Binder (PEG-PVA, Copovidone or HPMC Type 3	15	10
Kollidon® CL	22.5	10
Mg stearate	2.5	2
Total	500	332
Tablet diameter	12 mm	10 mm
Batch size	1.5 kg	1.3 kg

The fluid bed granulation was carried out on a Glatt GPC G3 with a 7.5% binder solution at a spray rate of 30 g/min with inlet air and outlet air temperatures of 50 °C and 27 °C, respectively. The high shear granulation was carried out on a mixer granulator (Stephan mixer) with 15% binder solution for about 12 minutes at a propeller speed of 800 ppm. The resulting granules were dried and sieved through 0.8 mm sieve.

Figure 3 illustrates the hardness of ascorbic tablets as a function of compression force. Apparently, the hardness increased as the compression force increased for both granules prepared either by fluid bed or by high shear mixer. This was also true for the placebo formulation (data not shown). As expected, the fluid bed granules were more compressible as compared to those prepared by high shear mixers, presumably due to their higher porosity and rougher surface structure. The hardness of tablets from fluid bed granules was about 50-100% higher than those prepared by high shear granulation at a respective compression force. However, in mixer granulation PEG-PVA resulted in the highest hardness whereas in fluid bed granulation the copovidone outperformed.

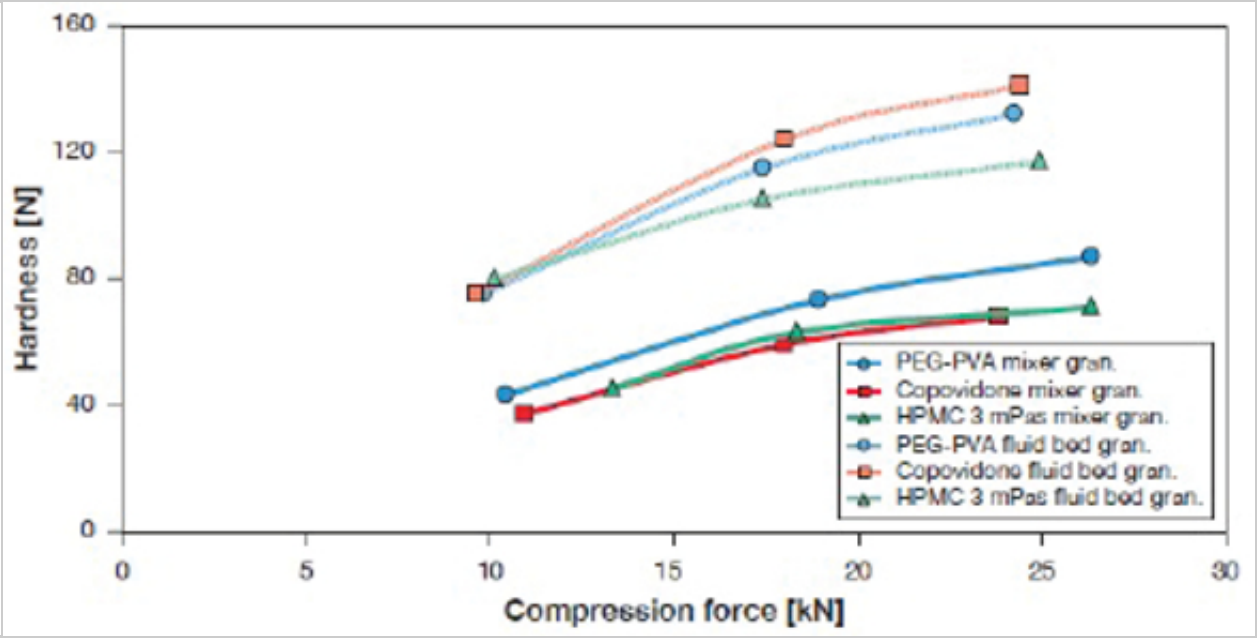

Figure 3. Hardness of ascorbic acid tablets with different binders used in fluid bed and high shear mixer granulations

Table 7 shows the powder characteristics of ascorbic acid granules prepared by fluid bed and high shear granulation. The properties of ascorbic acid granules were similar for each binder using the same granulation technology. When the two granulation technologies are compared, as expected, fluid bed granulation resulted in smaller granules of a lower bulk density. The placebo granules prepared with corresponding PEG-PVA, copovidone and HPMC Type 3 were also similar in properties to the ascorbic acid granules. The disintegration time of these placebo tablets ranged between 1 min and 3:30 min at all compression forces examined (10-25 kN), (data not shown).

Table 7. Properties of ascorbic acid granules prepared with diff erent binders by mixer and fl uid bed granulation

Property	Powder blend*	PEG-PVA		Copovidone		HPMC Type 3	
		Mixer	Fluid bed	Mixer	Fluid bed	Mixer	Fluid bed
Loss on drying		3%	2.7%	2.3%	2.9%	2.2%	3.1%
Angle of repose	40°	32.6°	34.3°	31.9°	35.8°	32.2°	35.4°
Flow time	Block	8.2 sec	7.8 sec	7.4 sec	8.2 sec	6.6 sec	7.8 sec
Mean particle size, [4,3]	92 µ	397 µ	162 µ	355 µ	148 µ	398 µ	189 µ
Bulk density	0.45 g/ml	0.57 g/ml	0.43 g/ml	0.57 g/ml	0.43 g/ml	0.57 g/ml	0.34 g/ml
*Prepared by direct blending without granulation							

Peroxides in PEG-PVA: A Stability Study

PEG-PVA batches were used to monitor the peroxide contents at different temperature and humidity conditions. *Table 8* exhibits the level of peroxides in PEG-PVA batches under different stability conditions.

Table 8. Stability of PEG-PVA to monitor the peroxide contents (denoted in mEq/kg*)

Stability condition	0 Month, mEq/kg	3 month, mEq/kg	6 month, mEq/kg	12 month, mEq/kg	18 month, mEq// kg
Room temp.	1				
25 °C/60% RH		< 1	< 1	4	3
30 °C/35% RH		< 1	< 1	2	-
30 °C/70% RH		< 1	< 1	1	-
40 °C/75% RH		< 1	< 1	1	1
25 °C/closed		< 1	< 1	< 1	-
30 °C/closed		< 1	< 1	< 1	-
40 °C/closed		< 1	< 1	< 1	-
* mEq/kg is equivalent to 17 ppm (based on 0.5 of the molecular weight of hydrogen peroxide)					

The data demonstrate that the peroxide contents remained very low under all ICH conditions investigated, suggesting

that the PEG-PVA is essentially free of peroxides not only at the ambient stability conditions of 25 °C and 30 °C but also under the accelerated condition of 40 °C/75% RH. In addition, the peroxide level was unchanged and remained at <1 meq/kg in the closed system at all temperatures, 25 °C, 30 °C and 40 °C.

Discussion

PEG-PVA has been used as an instant release coating polymer of soluble and insoluble drugs[13]. The unique coating property with a greater film flexibility, as often required for coatings, stems from the polyethylene glycol moiety that is grafted with polyvinyl alcohol moieties via covalent linkages. PEG-PVA does not require a plasticizer, improves coating time and saves cost, and enables stronger adherence to a variety of tablets surfaces comprised of MCC, lactose, starch and wax as compared to cellulosic coating polymers[14-16]. PEG-PVA is also used as a pore former in coatings[17-19]. Furthermore, with additional 40% PVA (PEG-PVA/PVA) it provides an extraordinary moisture barrier for highly sensitive APIs14. Surprisingly, gastroretentive and floating tablets can be formulated based on this polymer[20]. PEG-PVA is compatible to pharmaceutically accepted pigments, and hence, is used in PVA-based coating systems for SODF.

The principal suitability of PEG-PVA as a binder has already been investigated[12,21]. This article, however, describes the use of the highly functional PEG-PVA as a wet binder in granulation of placebo and an API's formulations. In a high shear granulation study, the particle size distribution of PEG-PVA granules was more homogeneous as compared to granules obtained with povidones K25 and K90, and the tensile strengths of tablets were also slightly improved at binder concentrations of 1.5%-5.0%[22]. Thus, the binding properties of PEGPVA are comparable with commonly used binders such as povidone K-30, copovidone and HPMC. Amongst several physicochemical properties, the lack of peroxides in PEG-PVA, adds a new innovative dimension in protecting highly sensitive drug molecules.

The wet granulation data with PEG-PVA as a binder shows that not only granule characteristics but also tablet properties are comparable to other binders such as povidone K30 and copovidone. The fact that various tablet compositions as well as two different granulation technologies have been used, supports this general statement. Particular benefits exerted with PEG-PVA in the hardness of tablets made by mixer granulation where it outperformed other binders. In fluid bed granulation copovidone resulted in a slightly higher hardness. It was not surprising that granules made in a fluid bed had a higher compressibility than those from mixer granulation due to a less densely packing, higher porosity and smaller granule size. It is supposed that due to the enormous elongation at break of PEG-PVA films (approximately 100%) it is particularly suitable for the granulation of brittle compounds.

Suhrenbrock et al. investigated PEG-PVA as a binder in drug layering of MCC pellets[23]. PEG-PVA has also been investigated in solid dispersions of itraconazole by melt extrusion[24]. This study is aimed at understanding the extrusion behavior of PEG-PVA with increasing drug loadings. The authors concluded that 30% itraconazole was miscible in the polymer while increasing the amount to 40%, resulted in precipitation and phase separation of drug in the PEG-PVA matrix. In a separate study, solid dispersions of miconazole were prepared with PEGPVA as a carrier by melt extrusion and the miscibility of the drug was investigated on the extrudates prepared by a laboratory scale simple screw design and a pilot scale extruder under similar extrusion conditions. The authors observed a phase separation with increasing drug loading[25]. Thus, polymeric matrices like PEG-PVA might be critical for preparation of amorphous solid dispersions with a higher drug loading, especially in hot melt extrusion (HME). However, the selection of a polymer like PEG-PVA could be relevant to those APIs sensitive to peroxides to avoid oxidative degradation.

Oxidative degradation of APIs has been subject of continued interest[7-9,26,27]. Hartauer et al., for instance, have demonstrated that the tertiary amine of raloxifene was highly sensitive to residual peroxides in povidone (binder) and crospovidone (disintegrant), which caused the oxidation of API to N-oxide[7]. The authors also demonstrated that with

increasing amounts of peroxides (spiked with hydrogen peroxide), the amount of N-oxide increased, suggesting that the presence of peroxides could lead to significant losses in the efficacy of the drug. Taken collectively, the residual peroxides will increase as time progresses, and if not controlled, could even be challenging and is often practically impossible to maintain the lower peroxide levels, unless controlled by addition of antioxidants or using the appropriate packaging [28, 29]. PEG-PVA might be able to overcome these challenges without using an antioxidant or a smarter packaging. Fussnegger et al. have recently demonstrated that PEG-PVA behaved similar to low peroxide povidone K30 LP and polyethylene vinyl alcohol packaging povidone K30, and prevented the degradation of raloxifene to N-oxide when compared with povidones K29/32 and K30 at binder levels of 3% and 6%, supporting further that PEG-PVA is peroxide free[30]. As demonstrated in the stability studies, PEG-PVA is exceptionally stable and does not show a peroxide increase under various stability conditions.

Safety and Regulatory Status of PEG-PVA

PEG-PVA is monographed in United States, European and Japanese Pharmacopeias. It has been approved in drug products in many countries around the globe. The first approval of drug containing PEG-PVA occurred with the acceptance of 1000 mg metformin tablets in August 2005 by German health authorities (BfArM), which later followed the acceptances in other countries in Europe, Japan and the US. The first FDA approval of a drug containing PEG-PVA was granted in April 2008 for 200 mg ibuprofen tablets. A daily intake of about 9 mg/kg body weight in human is calculated based on NOAEL value in toxicological studies of approximately 900 mg and using a safety factor of 100. PEG-PVA has also been listed in FDA's inactive ingredient database (IID) at a maximum potency of 25 mg per dose in the extended release oral tablets.

The US DMFs IV (CMC) and V (safety) are available. A food additive petition (FAP) has been accepted by the FDA to qualify it as generally regarded as safe (GRAS) excipient.

Conclusion

PEG-PVA exhibits an excellent binding characteristic upon granulation in both fluid bed and high shear granulation processes. Our data suggests that the physical properties of PEG-PVA granules and of compressed tablets are comparable with the commonly used binders such as povidone K-30, copovidone and HPMC. In mixer granulation, PEG-PVA outperformed other binders with regard to hardness of tablets. The stability data reveal that the inherent peroxide level does not increase at ambient or accelerated stability conditions. Taken together, the PEGPVA is a peroxide-free excipient and is highly applicable as a wet binder in development of SODF, especially, for those low dose APIs highly sensitive to oxidative degradation.

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Author Biographies

Shaukat Ali *has over 21 years of experience in the pharmaceutical industries including 11 years at BASF, where he supports solubilization, instant and modified release platforms, and APIs. Dr. Ali's areas of expertise include solid dispersions, liposome drug delivery, controlled release, transdermal, and film development technologies.*

Dr. Ali is a member of the editorial advisory boards of, American Pharmaceutical reviews, Biopharma Asia, Contract Pharma, Drug Delivery & Development, International Journal of Pharmaceutical Investigation, Journal of Pharmaceutical Sciences and Pharmacology, and Journal of Analytical & Pharmaceutical Research. He is also a member of USP panel of experts for General Chapters-Physical Analysis. He received his Ph.D. in Chemistry from the City University of New York and pursued his postdoctoral training at the University of Minnesota and Cornell University. He has authored over 37 scientific articles and is the inventor in 14 US patents.

Bernhard Fussnegger *has over 25 years of experience in the excipients business of BASF. Presently he is in charge of product development activities as well as the instant and modified release platform. In this area, he is responsible for technical aspects of excipients manufactured internally and externally of BASF.*

Dr. Fussnegger is a member of several expert panels including the chair of the USP expert panel on Povidones, vice-chair of the pharmacopoeial review and harmonization committee of IPEC Europe, and he is delegate of IPEC Europe in the IPEC/PDG discussions on harmonization efforts for excipients. He received his PhD in food chemistry from the Technical University of Stuttgart, Germany. He has authored several scientific articles and is the inventor in more than 20 patents.

***Karl Kolter**, after having worked for 7 years at Knoll AG in Ludwigshafen, joined BASF AG in 1993, where he has been responsible for R&D activities in pharmaceutical excipients, drug formulations and the application technology of vitamins and carotenoids for pharma and food. Dr. Kolter's current work is the development of innovative excipients mainly for solid oral dosage forms, which has already resulted in various new products in the Kollicoat® and Kollidon® range (Kollicoat® MAE 30 D, 100P, SR 30 D, IR, IR White, Protect, Kollidon® SR, CL-F, CL-SF, Ludipress® LCE).*

He obtained his Ph. D. in pharmaceutical chemistry at the University of Mainz, Germany. He has published more than 100 articles and posters, and is the inventor in 90 patents.

- **Excipients »**
- **Pharmaceutical Raw Materials and APIs »**